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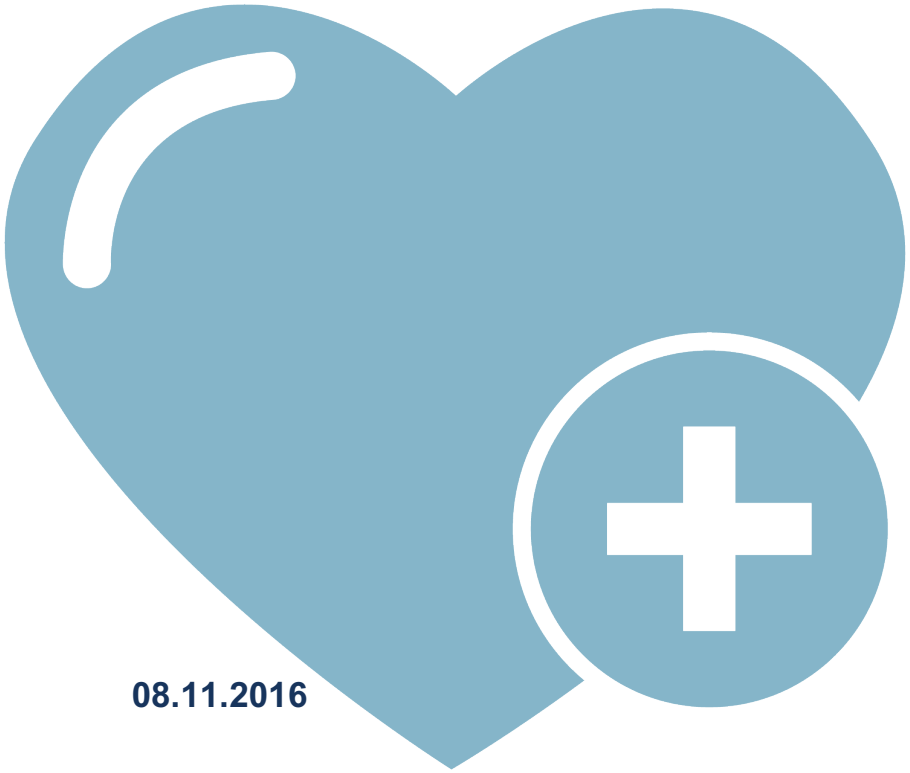
Grants Working Group Public Review Summary

Clinical Evaluation of Improved Configurations of the Delivery Device Component of an Islet Cell Replacement Therapy for Type 1 Diabetes

Application Number: CLIN2-08839	Review Date: July 26, 2016

Clinical Trial Stage Project Proposal (CLIN2)



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Clinical Evaluation of Improved Configurations of the Delivery Device Component of an Islet Cell Replacement Therapy for Type 1 Diabetes

APPLICATION NUMBER: CLIN2-08839

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate

The proposed clinical trial will test different configurations of empty macroencapsulation devices in order to optimize device configuration for use in a combination product consisting of human embryonic stem cell (hESC)-derived pancreatic progenitor cells in the macroencapsulation device.

Indication

Type 1 diabetes (T1D)

Unmet Medical Need

For the millions of people with T1D, the current standard of care is not sufficient. The product candidate will free patients from never ending vigilance, self-administration of insulin, risk of hypoglycemic coma or death, long-term complications, and significantly reduced life span.

Major Proposed Activities

Manufacturing and quality control with different configurations of encapsulation devices for the clinical trial

Enroll subjects in the clinical trial

Analyze clinical data

Funds Requested

$ 2,582,074 ($1,207,799 Co-funding)

Recommendation

Score: 1*

Votes for Score 1 = 5 GWG members

Votes for Score 2 = 5 GWG members

Votes for Score 3 = 1 GWG members

- A score of “1” means that the application has exceptional merit and warrants funding;
- A score of “2” means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement;
- A score of “3” means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG’s recommendation.
- * Under the current GWG bylaws, when there is a numerical tie between two scores, any member of the GWG may make a motion to assign the application to a score of “1”, “2”, or “3”. In this case, the GWG adopted a motion to assign a score of “1” by a vote of 9 (yes) -8 (no)-1 (abstention).

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Review Overview

Reviewers thought that the proposed combination product (hESC-derived pancreatic progenitor cells in an encapsulation device) could fulfill an unmet medical need in the treatment of patients with T1D and were supportive of continued development of this product. However, reviewers were split as to whether the proposed clinical trial will advance clinical development of the combination product. Some reviewers thought that the excellence of the team and the benefit of collecting additional clinical data outweigh concerns regarding the lack of strong preliminary data and shortcomings in the trial design and recommended the project for funding. Other reviewers thought the clinical development program would be better served by strengthening the preliminary data package and improving the trial design and then reapplying with an improved application. These reviewers did not recommend this project for funding.

Review Summary

Does the project hold the necessary significance and potential for impact?

a) Consider whether the proposed therapy fulfills an unmet medical need.

- T1D is clear unmet medical need.
- While the empty encapsulation devices that will be used in the proposed trial will not fulfill an unmet medical need, the combination product under development holds great promise to do so.

b) Consider whether the approach is likely to provide an improvement over the standard of care for the intended patient population.

- The combination product would provide a substantial improvement over the standard of care for the intended patient population if successfully developed.

c) Consider whether the proposed therapeutic offers a sufficient, impactful, and practical value proposition for patients and/or health care providers.

- If the combination product is able to appropriately regulate glucose in T1D without continual monitoring and medical intervention, the value proposition for patients and providers is sufficient, impactful, and practical.

Is the rationale sound?

a) Consider whether the proposed project is based on a sound scientific and/or clinical rationale, and whether it is supported by the body of available data.

- Reviewers were divided as to whether the proposed trial is supported by adequate preclinical data and is the appropriate next step.
    - Some reviewers thought that it was premature to test different device configurations in human clinical trials given the provided data package.
        - Overcoming the foreign body response is a daunting task attempted by many in the encapsulation field. The application did not include sufficient information regarding how and why materials for the devices were selected nor did it provide evidence that the proposed device design would decrease foreign body responses.
        - There is not sufficient data in the application for reviewers to

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think it is likely that any of the proposed configurations or different insertion sites will be successful in improving vascularization or decreasing the foreign body response to ultimately improve engraftment of the combination product.

- Conduct of initial studies in large animal models instead of humans would allow more systematic testing with different device configurations with and without cells and with more extensive immune studies than can be done in humans. Data from such a study would inform device design and support an improved clinical trial design and might be a faster route to success than executing the proposed trial.

- Other reviewers thought that initiation of a human clinical trial with the empty devices is appropriate and supported by data from the ongoing clinical trial with the combination product.
  - Animal models can be challenging due to xenograft immune response.
  - Immune responses in animal studies may differ from that observed in humans.
  - The applicant provided sufficient data to support moving forward with the proposed clinical trial.

- The team is overly optimistic in some of their assertions and projections. For example, the team proposes that the cells will be resistant to hypoxia, but reviewers thought such an assertion was overstated and not supported by sufficient data.

b) Consider whether the data supports the continued development of the therapeutic candidate at this stage.

- Reviewers were highly supportive of continued development of the combination product but were divided as to the likelihood that the proposed project would advance the development of the combination product.
- Reviewers would have liked to see additional information and data from the ongoing Phase 1 clinical trial in order to understand the current state of the program.
- The applicant understands they need to try a different approach to achieving engraftment with the combination product, and the data provided supports that this might be possible.

Is the project well planned and designed?

a) Consider whether the project is appropriately planned and designed to meet the objective of the program announcement and achieve meaningful outcomes to support further development of the therapeutic candidate.

- The applicant has identified problems in the ongoing clinical trial with the combination product and proposes a clinical trial to gain information on how to mitigate these problems. Reviewers were divided as to whether the proposed trial would yield such information.
  - The empty devices may not elicit the same immune response as the combination product and testing the devices without the cells may or may not be relevant to the combination product. The applicant does not adequately address this issue.
  - A better trial design might be to include patients receiving both the combination product and the empty devices. This would allow the

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applicant to better interpret the empty device data.

- The applicant is not proposing sufficient immune studies to capture all necessary data. The immune studies are focused on the explanted devices, and the applicant does not propose meaningful immune monitoring in the recipient.
- Inserting multiple devices of different configuration into a signal patient may be more appropriate for an animal study than a human study in order to gain sufficient information on the specificity of observed reactions.

- The proposed protocol design is complicated and tests different device configurations. There are a lot of variables and a small number of subjects resulting in a bit of shotgun approach to clinical testing. It is not clear, based on the proposed trial design, that statistically significant data will be gained that will meaningfully inform device selection.
- The team realizes they will need a lot of surface area and the appropriate site to get cell survival and engraftment and the devices are, therefore, large and they are trying a lot of insertion sites. This is the right direction, but it is not clear that the protocol design will deliver clear answers regarding which design and insertion site to pursue.

b) Consider whether this is a well-constructed, quality program.

- The overall program for development of the combination product is of high quality, but reviewers were divided as to whether the proposed project and strategies to mitigate obstacles to clinical development improve or worsen the quality of the overall program.

c) Consider whether the project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission.

- The timeline and project plan demonstrate an urgency commensurate with CIRM's mission.

Is the project feasible?

a) Consider whether the intended objectives are likely to be achieved within the proposed timeline.

- Reviewers thought it likely that the applicant could execute the study as proposed.

b) Consider whether the proposed team is appropriately qualified and staffed and whether the team has access to all the necessary resources to conduct the proposed activities.

- The project team is experienced and has demonstrated good operational capacity.
- The collaborators are excellent and these collaborations strengthen the proposal.

c) Consider whether the team has a viable contingency plan to manage risks and delays.

- Reviewers did not express concerns regarding the contingency plan.

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CIRM Recommendation to Application Review Subcommittee

The CIRM recommendation to the Application Review Subcommittee is considered after the GWG review and did not affect the GWG outcome or summary. This section will be posted publicly.

RECOMMENDATION: CIRM does not concur with the GWG recommendation. Although the recommendation is allowed by our current rules, a disposition of a "2" is more appropriate for this application because no plurality was reached by the scientific members of the GWG and a majority of scientific members scored the application below a score of "1". Applicants receiving a score of "2" are offered the opportunity to improve and resubmit the application for reconsideration immediately. CIRM intends to propose a modification of its rules at the September Board meeting to address this issue.